REMARKS

1. Status of Claims

Claims 8-29 are pending and stand rejected.

2. Amendment

The term "molecules" has been added after "cell surface receptor" in claim 8 in order to provide proper antecedent basis for that same language in claims 9 and 12. The Markush group language and layout of claim 18 has been amended to conform with claim 17 in parent application U.S. Serial No. 09/430,508. In particular, Applicant has rearranged claim 18 and deleted several occurrences of the term "and". Applicant has also taken the opportunity to correct some obvious typographical errors (i.e., two occurrences of "FGF-R" and "tryosine" instead of "tyrosine"). The nomenclature used to describe CD3 subunits has also been clarified (i.e., use of zeta, eta, gamma, delta and epsilon as set forth on page 9, lines 25-28). These amendments were made purely for clarification purposes, the scope of the claims remains unchanged. These amendment are also fully supported by the original claims and specification – no new matter has been added.

3. Rejection for Lack of Novelty

Claims 8-27 were rejected under 35 U.S.C. § 102(b) as being anticipated by Wold, Methods Enzymology 11:617-640, 1966. Claims 8-29 were rejected under 35 U.S.C. § 102(b) as being anticipated by Ji, Methods Enzymology 91:580-609, 1983. Applicant respectfully submits that Wold and Ji do not anticipate the pending claims because they both fail to teach each and every element of the claimed methods. MPEP § 2131.

Claims 8-18 and 28-29 recite methods that involve an agent that *binds* to two or more endogenous cell surface receptor molecules. Claims 19-27 and 28-29 recite methods that involve an agent that *binds* to two or more endogenous protein mediators. A skilled person in the art readily understands that the term "binds" is used in the art to refer to *non-covalent* associations (e.g., between an antibody and antigen or a receptor and a ligand). The explicit teachings of the application (e.g., see discussion of binding affinities K_d on page 11, lines 13-18; discussion of exemplary receptor binding moieties on page 13, lines 19-25; discussion of affinity assays for

identifying receptor binding moieties on pages 14-19; etc.) conform with this interpretation and reinforce that "binds" refers to non-covalent associations.

Wold and Ji do not teach methods that involve an agent that *binds* non-covalently to two or more endogenous protein mediators. Instead, both Wold and Ji teach bifunctional reagents that *react with* and thereby form *covalent* bridges within or between proteins. As explained by Wold (page 617) and Ji (page 580), these *covalent* bridges were used in the 1960s-1980s to study and determine the three dimensional structures of proteins and protein complexes.

Exemplary reagents that were reviewed by Wold in 1966 include *N*-substituted maleimide derivatives that *react* with sulfydryl groups (pages 622-623); alkyl halides that *react* with sulfydryl groups, sulfides, imidazole, and amino groups (pages 623-627); aryl halides that *react* with amino, tyrosine phenolic, sulfydryl and imidazole groups (pages 627-632); etc. All of these reagents react with groups that are present within proteins to form covalent bonds. Ji describes covalent crosslinking reagents that were developed after Wold's review. In particular, Ji describes covalent reagents that react with specific protein groups (page 591-601) and covalent reagents that include photoactivable (pages 602-605) or cleavable groups (page 606-607). Nowhere does Ji remedy the deficiencies of Wold by teaching methods for preparing an agent that *binds* non-covalently to two or more endogenous protein mediators.

For all of these reasons, Applicant respectfully submits that the pending claims are not anticipated by Wold or Ji. Withdrawal of these rejections is earnestly requested.

4. Rejection for Lack of Written Description

This application is a divisional of U.S. Serial No. 09/430,508 that is currently being examined by Examiner Lambertson. The claims in the parent and divisional applications have been rejected for lack of written description and the arguments presented by Examiners Lambertson and Vogel in these two related cases are very similar. Mr. David Berstein, Dr. Brenda Herschbach Jarrell and the undersigned agent, held a telephone interview with Examiner Lambertson on March 24, 2005 and discussed the written description in the context of the *parent* case. Although no ultimate agreement was reached, a number of arguments (both old and new) were discussed and progress was made. Since the rejections in both cases are so similar, Applicant is hereby presenting arguments that parallel those being filed under separate cover in the parent application. All arguments already of record that are not reiterated in this Response are incorporated herein by reference.

The pending claims stand rejected for lack of written description. In particular, the Examiner states that the disclosure in the specification does not reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. This rejection is respectfully traversed; reconsideration and withdrawal is requested.

The written description requirement imposes a duty on patent applicants to notify the public of the scope and content of their inventions. The requirement is satisfied if one skilled in the art would reasonably conclude that the inventors were in possession of the claimed invention at the time the patent application was filed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555 (Fed. Cir. 1991). See also Guidelines for Examination of Patent Applications under the 35 U.S.C. § 112, ¶ 1, "Written Description" Requirement, 66 Fed. Reg. 4, 1099 (2001). A determination of whether the written description requirement is satisfied requires reading the disclosure in light of the knowledge possessed by those skilled in the art at the time that the application was filed. *In re Alton*, 76 F.3d 1168 (Fed. Cir. 1996).

This application claims methods for preparing certain oligomerizing agents that effect biological events mediated by the association of protein mediators. The oligomerizing agents bind and thereby cause the protein mediators to associate.

As a preliminary matter, Applicant notes that, as set forth in the disclosure (see for example page 9, lines 6-8), it was well established in the art at the time the application was filed that the relevant biological events *necessarily occur* whenever the appropriate proteins are associated. Only imprecise association is required. Applicant has therefore argued that a description of *binding* is by necessity also a description of *effecting*.

Applicant encloses evidence that the correlation between *binding* and *effecting* was known in the art at the time of filing. In particular, Applicant encloses a reference by Spaargaren et al. demonstrating (in 1991, see Exhibit A) that a variety of different bivalent antibodies to the EGF receptor all successfully activated the receptor. The different antibodies recognized different epitopes on the receptor and therefore presumably bound in different ways from one another, as well as from its natural ligand. However, any binding that accomplished oligomerization also achieved activation. Previously cited references by Watowich et al. (see page 9, lines 8-12, Exhibit B) and Fuh et al. (see page 9, lines 12-15, Exhibit C) similarly demonstrated (in 1992) activation of EPO receptors and GH receptors, respectively, through association achieved by engineered disulfide bonds or bivalent antibodies. In each of these

references, association, regardless of how achieved, effected a biological event. As further evidence that this correlation was recognized in the art, Applicant encloses a 1994 article by Austin et al. (see Exhibit D) that states (in the context of the present invention):

> "It is easy to imagine the mixing and matching of different protein-binding surfaces using synthetic organic chemistry, to create new dimerizers with tailor made properties. Since protein dimerizers simply create a high local concentration of a particular protein at a particular cellular location, *their actions will not require the geometric precision associated with allosteric agents*." (see page 136, *emphasis* added)

Thus, Applicant respectfully submits that association of protein mediators triggers their activation and therefore, for the purposes of the present written description question, a description of *binding* is necessarily a description of *effecting* in the context of the present claims.

Given that *binding* and *effecting* are simultaneously described in the present case, Applicant urges that the written description standard articulated explicitly for antibodies is equally applicable here. That is, in *Noelle v. Lederman*, 355 F.3d 1343 (Fed. Cir. 2004), the Federal Circuit held that "as long as an applicant has disclosed a 'fully characterized antigen,' either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, *the applicant can claim an antibody by its binding affinity to that described antigen*" (*emphasis* added). *Id.* at 1349. Thus, when the antigen is fully defined, the antibody is also described.

In *Noelle*, the patent applicant ultimately failed to satisfy the written description requirement because he had failed to isolate and thereby characterize the antigen. *Id.* In the present case, there is no dispute that the target is fully defined (e.g., see the description of representative protein mediators on pages 7-11 and references cited therein). The Examiner may resist application of the *Noelle* standard, however, on the ground that antibodies are all structurally related, whereas the present claims encompass use of oligomerizing agents with different chemical structures.

Applicant respectfully submits that this analysis misses the point. It is correct that antibodies, as a class of molecules, have structural similarities. However, these similarities are irrelevant to their binding capabilities. In fact, the portion of an antibody that is responsible for

its binding attributes is referred to as the *variable* portion precisely because its amino acid sequence *differs* from that of other antibodies. It is not possible in advance to determine which variable region sequences will allow an antibody to bind to a particular antigen. Thus, the overall structural similarities of antibodies as a class of molecules cannot, by itself, be determinative of written description. In fact, the court in *Noelle*, echoing the USPTO Written Description guidelines, listed at least two other factors as being relevant – "the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature". *Id.*

Applicant respectfully submits that consideration of these factors reveals the strong parallels between the present situation and the antibody case addressed in *Noelle*. Specifically, the "functional characteristics" in *Noelle* were the ability of the antibodies to bind to a known antigen. In this case, the oligomerizing agents are small molecule ligands that bind to a known target. The parallels are clear and inescapable.

Applicant respectfully submits that the *Noelle* court's reference to antibody technology as "well developed and mature" must rest on the conclusion that those of ordinary skill in the art could be confident in advance that, given a well characterized antigen, they would be able to identify and produce antibodies that bind to it. The same holds true in the present case. Technologies for identifying small molecule ligands that bind to a given target were well established at the time the present application was filed. A variety of such agents were already known and available (see, for example, page 14 of the specification). As discussed in the 1994 review article by Gordon et al. (see Exhibit E, especially pages 1390-1392), combinatorial libraries of agents were being developed (see also Bunin et al., Exhibit F and DeWitt et al., Exhibit G that are cited by Gordon et al.). A whole host of binding assays for screening these diverse agents were also known (see, for example, pages 15-19 of the specification). In fact, high-throughput screening systems for identification of binding agents were being used at the time the present application was filed. As evidence of this, Applicant encloses a review by Burch et al. (see Exhibit H) that discusses the state of high-throughput screening methods in 1991. The 1994 review article by Gordon et al. is also relevant (see Exhibit E, especially pages 1393-1397). Thus, at the time the present application was filed, the starting materials and technology for identifying binding moieties and thus oligomerizing agents that bind to a known, defined target, were both established.

Furthermore, Applicant respectfully submits that a person skilled in the art would recognize in advance that for any given protein mediator many suitable binding moieties and oligomerizing agents will exist. Thus, as with antibodies, the universe of suitable binding moieties that one has to choose from is large and there are in effect *multiple* correct answers to the same question. The practitioner need only identify one of these answers. This is in stark contrast to inventions involving a single gene or protein where the search is for a unique entity with a unique structure. In those cases there is only a *single* correct answer.

The Examiner may argue that the technology for identifying binding moieties and oligomerizing agents was not as well established as the technology for identifying antibody binding agents because antibodies can all be made the same way (i.e., using hybridomas), whereas individual oligomerizing agents may require very different, sometimes complex, syntheses that are not described in the specification. Applicant respectfully submits that the proper question is not whether the present specification describes how to make every oligomerizing agent encompassed by the claims, but rather whether a person of ordinary skill in the art, reading the specification, would understand that the inventors were "in possession of" the claimed invention. That is, would a person of ordinary skill in the art have understood that the invention could successfully be practiced, based on the specification, to the full scope claimed? To this question, the answer is clearly "yes".

First, Applicant points out that the specification includes reference to a variety of binding agents (e.g., benzodiazepines, prostaglandins, beta-turn mimetics, alpha- and beta-blockers, etc. on page 14, lines 7-11 of the specification) that were available at the time the application was filed, and that were known to bind protein mediators of biological events. Collections of synthetic compounds and combinatorial libraries of compounds were also available (see page 19, lines 1-2 and Exhibits E-G). The specification also defines the characteristics that could be used to test other agents for desirable binding ability (see, for example, pages 15-19). Thus, a huge number of useful agents were already known and available in the art; others could readily be identified as they came available. No further guidance is required to describe possession of the invention.

Applicant has previously provided objective *evidence* that those of ordinary skill in the art, presented with teachings of the type found in the present specification, immediately recognize their generality and breadth, even when only limited exemplification is provided.

Specifically, Applicant has cited references by Qureshi and Tian, published after the filing of the present case, that report examples of oligomerizing agents of the type whose preparation is encompassed by the present claims. Qureshi provides a single example of an oligomerizing agent that dimerized the EPO receptor and concluded that "most cytokine receptors can be ligated together in an active conformation by a nonpeptidyl molecule" (last sentence, page 12161); Tian tested a single oligomerizing agent that dimerized the G-CSF receptor and concluded that "a small molecule can trigger the activation of a large (~120 kD) receptor protein that requires dimerization for activation" (last sentence, page 259). In each case, a single example justified broad conclusions because those of ordinary skill in the art immediately understood it would work more broadly, that Qureshi and Tian were "in possession of" broad discoveries.

Of further note, both Qureshi and Tian identified their binding agents by screening libraries of known compounds using a high-throughput assay for each receptor (see page 12158 of Qureshi and page 257 of Tian). Qureshi screened known antagonists of the EPO receptor and then linked eight copies of a preferred antagonist together to form an oligomerizing agent. Tian screened libraries of small molecules directly for oligomerizing agents. While both agents were identified after the present application was filed, the routine methods used reinforce the fact that the identification of binding agents is no more burdensome than the preparation of antibodies. This was recognized in a 1999 article by Clemons commenting that Tian's work suggested "the synthetic attainability of a wide range of receptor dimerizers" and conclusively showed that synthetic nonpeptidyl ligands can mimic the effects of polypeptide growth factors (see Exhibit I, especially page 114).

The Examiner has repeatedly rejected Applicant's arguments with regard to Qureshi and Tian on the ground that the particular agents used by Qureshi and Tian were not described in the specification and therefore cannot be relied upon as evidence that the present specification teaches a sufficient number of representative examples. Applicant does not rely on Qureshi and Tian as evidence that the present specification teaches a sufficient number of representative examples. Applicant refers to the specification and knowledge in the prior art to make that point. Rather, Applicant relies on Qureshi and Tian to provide objective evidence that only a small number of specific examples (only one!) is required to describe the present invention to those of ordinary skill in the art. The present specification contains abundant description, and fully

satisfies the written description requirement.

5. Conclusion

Applicant concludes with the belief that the claims as amended herein are free of the prior art and fully supported by the specification. Allowance of the claims as amended is earnestly requested.

Respectfully submitted,

Charles E. Lyon, D.Phil.
Agent for Applicant
Registration Number 56,630

CHOATE, HALL & STEWART, LLP
Exchange Place
53 State Street
Boston, MA 02109
(617) 248-5000